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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/935,168	08/21/2001	Jennifer L. West	RICE 103	9212

23579 7590 09/02/2003

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/935,168	WEST ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the c rresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *3-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2 and 6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-9 are pending.

2. Claims 3-5 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. It is noted that Applicant attempt to rejoin claims 3-5 in the elected invention of Group I (claims 1-2, and 6-9) which drawn to a method for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells bound to the scaffold using the matrix-enhancing molecule TGFβ. However, the methods of claims 3-5 are drawn to various method for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells bound to the scaffold using distinct matrix-enhancing molecule such as angiotensin II, insulin-like growth factor, or ascorbic acid that differ with respect to their biochemical structure and function. Further, the method of making versus the method of repairing or implanting a tissue engineering scaffold matrix using distinct matrix enhancing molecule such as angiotensin II, insulin-like growth factor, or ascorbic acid differ with their respect to their process steps and endpoints. Therefore, they are patentably. Finally, claims 3-5 have been restricted in groups and not species. There is no species requirement in the restriction mailed 9/24/02.

4. In view of the amendment filed 4/3/03, the following rejections remain.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-2, and 6-9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/23740 (Oct 1994, PTO 1449) in view of Dinbergs *et al* (J Biol Chem 271(47): 29822-29, 1996; PTO 892).

The WO 94/23740 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ or TGFβ2 covalently crosslinked to a polymer matrix such as polyethylene glycol having a molecule weight such as 5000 (M-S-PEG 5000) which is between 2000 and 6000 via tethers such as succinimydyl succinate and is in a density of 5.2 (See page 12, line 11, PEG-TGF-β conjugates, rhTGF- TGF-β2 (PEG5000) bridging page 13, in particular). The WO 94/23740 publication teaches the method of making a tissue engineering scaffold comprising coupling TGFβ to a polymer is useful for stimulation of bone formation at a lower dose (See abstract, in particular).

The claimed invention in claim 1 differs from the reference only that the method for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells bound to the scaffold comprising coupling matrix-enhancing molecules to the scaffold in an effective density to elicit production of extracellular matrix without increasing cellular proliferation wherein the matrix enhancing molecules are TGF-β is in a density between 1 and 100 ng/ml or in a concentration between about 4×10^{-6} to 4×10^{-3} nmol/ml.

The claimed invention in claim 2 differs from the reference only that the method further comprising attaching cells to the scaffold.

The claimed invention in claim 7 differs from the reference only that the method wherein the scaffold is a hydrogel.

The claimed invention in claim 8 differs from the reference only that the method wherein the hydrogel is a formed of a polymer selected from the group consisting of alginate, collagen, hyaluronic acid and polyethylene glycol polymers.

The claimed invention in claim 9 differs from the reference only that the method wherein the matrix enhancing molecules are TGF-β is in a concentration between about 4×10^{-6} to 4×10^{-3} nmol/ml.

Dinbergs *et al* teach a method for making a tissue engineering scaffold such as alginate/heparin-sepharose microsphere for inducing formation of extracellular matrix by cells such as endothelial cells and smooth muscle cells bound to said scaffold comprising coupling various matrix-enhancing molecule such as bFGF or TGFβ in a concentration 1-10 ng/ml (See Alginate/Heparin-Sepharose Microsphere Preparation and Growth Factor Incorporation, page 29823, column 2, bridging page 29824 column 1, in particular). The reference TGFβ is effective to elicit production of extracellular matrix (see page 29822, column 2, last paragraph, in particular) without increasing cellular proliferation (See Fig 2B, Fig 3B, Abstract, in particular). Dinbergs *et al* teach TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogels such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the TGF-beta-2 or the polyethylene glycol as taught by the WO 94/23740 publication for the TGFβ at a concentration of 1-10 ng/ml or the hydrogel such as alginate as taught by Dinbergs *et al* for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell or endothelial cells bound to the scaffold as taught by the WO 94/23740 publication and Dinbergs *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 94/23740 publication teaches the method of making a tissue engineering scaffold comprising coupling TGFβ to a polymer is useful for stimulation of bone formation at a lower dose (See abstract, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular). The term about is open-ended. It expands the claimed concentration to include the reference concentration of 1-10 ng/ml, which is about 4×10^{-6} to 4×10^{-3} nmol/ml. It is within the purview of one skilled in the art to apply the effective amount of TGFβ for inducing the formation of extra-cellular matrix without increasing cellular proliferation as taught by Dinbergs *et al.*

Applicants' arguments filed 4/3/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) bone formation requires cellular proliferation. There is no teaching in the WO 94/23740 of increasing the amount of the extracellular matrix. (2) the claims are drawn to a method wherein (1) growth factor is coupled to a polymeric scaffold note not a polymer in a solution; (2) the density of the growth factor does not cause an increase in cellular proliferation. (3) Dinhergs et al demonstrate that cellular proliferation is increased by continuous delivery of TGFβ in solution compared to bolus administration. Figure 3B illustrates the effect of controlled release of TGFβ on smooth muscle cell count as a function of time and clearly demonstrated increased cell proliferation.

In response to applicant's argument that the WO 94/23740 does not teach increasing the amount of the extracellular matrix, it would have been a rejection under 35 USC 102 (b) if WO 94/23740 publication teaches ever limitation of the claims. Further, the "bone formation requires cellular proliferation" is not recited in the claims. The WO 94/23740 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ or TGFβ2 covalently crosslinked to a polymer matrix such as polyethylene glycol having a molecule weight such as 5000 (M-S-PEG 5000) which is between 2000 and 6000 via tethers such as succinimydyl succinate and is in a density of 5.2 (See page 12, line 11, PEG-TGF-β conjugates, rhTGF- TGF-β2 (PEG5000) bridging page 13, in particular). The WO 94/23740 publication teaches that the method of making a tissue engineering scaffold comprising coupling TGFβ to a polymer is useful for stimulation of bone formation at a lower dose (See abstract, in particular).

In response to applicant's argument that Dinhergs et al demonstrate that cellular proliferation is increased by continuous delivery of TGFβ in solution compared to bolus administration. Figure 3B illustrates the effect of controlled release of TGFβ on smooth muscle cell count as a function of time and clearly demonstrated increased cell proliferation. However, the reference Figure 3A demonstrates that matrix enhancing molecule such as TGFβ when coupling to the reference matrix inhibits endothelial cell proliferation in smooth muscle cell and inhibiting muscle cell proliferation (Figure 3B) over a two days period. Base claim 1 merely recites a method for making a tissue engineering scaffold formation of extracellular matrix by any cells bound to the scaffold using TGFβ coupling to the matrix wherein the coupling matrix-enhancing molecules to the scaffold elicit production of extracellular matrix without increasing

cellular proliferation. The claim does not recite any specific cell type that bound to the claimed matrix. Further, the term "without increasing proliferation" is not the same as inhibits cellular proliferation since without increasing proliferation means there is still some proliferation albeit to a lesser extend. It is within the teaching of the Dinhergs et al because inhibition of cellular proliferation depends on the specific cell types and duration of exposure. The reference teaching clearly demonstrated the lack of "increasing" proliferation over a two days period (Figures 3A-B). The reference matrix-enhancing molecule is the same matrix-enhancing molecule in instant claim 1.

8. Claims 1-2, and 6-9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/27657 (Sept 1996; PTO 1449) in view of Dinbergs *et al* (J Biol Chem 271(47): 29822-29, 1996; PTO 892).

The WO 96/27657 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ (see page 10, claim 25 of WO 96/27657 publication, in particular) flexibly linked or tethers (See page 6, line 11, page 12, Attachment methods, in particular) using carbodiimides as cross-linker to a polymer matrix such as hyaluronic acid (see page 7, line 1, in particular) or collagen, or polyethylene oxide, alginate, (See page 17, line 8, in particular) which all inherently have a molecular weight between 2000 and 5000 (See claims 22-23 of WO 96/27657 publication, in particular). The reference method further attaching cells to the reference scaffold (See page 16, line 7, in particular) for constructing tissue regeneration such as production of extracellular matrix proteins such as collagen (See page 17, line 1-4, in particular). The WO 96/27657 publication teaches the growth factor is localized to desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular).

The claimed invention in claims 1 and 9 differs from the reference only that the method for wherein the matrix enhancing molecules are TGF-β is in a density between 1 and 100 ng/ml or in a concentration between about 4×10^{-6} to 4×10^{-3} nmol/ml.

Dinbergs *et al* teach a method for making a tissue engineering scaffold such as alginate/heparin-sepharose microsphere for inducing formation of extracellular matrix by cells such as endothelial cells and smooth muscle cells bound to said scaffold comprising coupling various matrix-enhancing molecule such as bFGF or TGFβ in a concentration 1-10 ng/ml (See Alginate/Heparin-Sepharose Microsphere Preparation and Growth Factor Incorporation, page

29823, column 2, bridging page 29824 column 1, in particular). The reference TGFβ is effective to elicit production of extracellular matrix (see page 29822, column 2, last paragraph, in particular) without increasing cellular proliferation over the 2 days (See Fig 2B, Fig 3B, Abstract, in particular). Dinbergs *et al* teach TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogels such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include TGFβ at a concentration of about 1-10 ng/ml as taught by Dinbergs *et al* for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell or endothelial cells bound to the scaffold as taught by the WO 96/27657 publication and Dinbergs *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 96/27657 publication teaches the growth factor is localized to desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular). The term about is open-ended. It expands the claimed concentration to include the reference concentration of 1-10 ng/ml, which is about 4×10^{-6} to 4×10^{-3} nmol/ml. It is within the purview of one skilled in the art to apply the effective amount of TGFβ for inducing the formation of extra-cellular matrix without increasing cellular proliferation as taught by Dinbergs *et al.*

Applicants' arguments filed 4/3/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) this rejection is treated as a rejection under 35 USC 103 since a rejection under 102(b) requires all claimed elements to be presented in a single reference. (2) neither the cited references discloses any method of increasing extracellular without increasing cellular proliferation. (3) There is no suggestion in either reference to incorporate the

teachings of the other reference. (4) Even if the teachings of the references are combined, the combination does not suggest the claimed method because it does not suggest attaching growth factors to a polymeric matrix via tethers in a concentration effective to enhance extracellular matrix formation without an increase in cellular proliferation. (5) The claimed methods have unexpected results in view of Dingbergs et al. The result is unexpected in view of the prior art and therefore not obvious to one with ordinary skill in the art.

In response, Applicant's assumption is correct that this rejection is under 35 USC 103 and not under 35 USC 102(b). The examiner apology for the inadvertent typographical error.

In response to applicant's argument that neither the cited reference discloses any method of increasing production of extracellular matrix without increasing cellular proliferation, Dinhergs et al demonstrate that coupling of the reference matrix-enhancing molecule such as TGFβ to the reference matrix inhibits endothelial cell proliferation in smooth muscle cell (Figure 3A) and inhibiting smooth muscle cell proliferation over a two days period (Figure 3B). Base claim 1 merely recites a method for making a tissue engineering scaffold formation of extracellular matrix by any cells bound to the scaffold using TGFβ coupling to the matrix wherein the coupling matrix-enhancing molecules to the scaffold elicit production of extracellular matrix without increasing cellular proliferation. The claim does not recite any specific cell that bound to the claimed matrix. Further, the term "without increasing proliferation" is not the same as inhibits cellular proliferation albeit to a lesser extend. It is within the teaching of the Dinhergs et al because inhibition of cellular proliferation depends on the specific cell types and the reference teaching clearly demonstrated the lack of "increasing" proliferation (Figure 3A). The reference matrix-enhancing molecule is the same matrix-enhancing molecule in instant claim 1. It is within the purview of one of ordinary skill in the art at the time the invention was made to increase the concentration of the reference TGFβ to inhibit cellular proliferation such as bolus administration.

In response to applicant's argument that there is no suggestion in either reference to incorporate the teachings of the other reference, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). The examiner recognizes that obviousness can only be established by combining

or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom. In re Preda, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). See MPEP 2144.01

In response to applicant's reliance on unexpected results, the record does not contain sufficient objective evidence that the claimed method produced unexpected results such as without increasing cellular proliferation. In fact, the results of the claimed method as showed in page 14 and Figure 4 of the specification indicate that cell numbers did not increase over the 2 days, despite changes in matrix production per cell. Dinbergs *et al* teach a method for making a tissue engineering scaffold such as alginate/heparin-sepharose microsphere for inducing formation of extracellular matrix by cells such as endothelial cells and smooth muscle cells bound to said scaffold comprising coupling various matrix-enhancing molecule such as bFGF or TGFβ in a concentration 1-10 ng/ml (See Alginate/Heparin-Sepharose Microsphere Preparation and Growth Factor Incorporation, page 29823, column 2, bridging page 29824 column 1, in particular). The reference TGFβ is effective to elicit production of extracellular matrix (see page 29822, column 2, last paragraph, in particular) without increasing cellular proliferation over the 2 days (See Fig 2B, Fig 3A and 3B, Abstract, in particular).

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

12. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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